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14
REVIEW NO.

EEB BRANCH REVIEW

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TYPE PRODUCT(S): I, D, H, F, N, R, S Fungicide

DATA ACCESSION NO(S).

PRODUCT MANAGER NO. H. Jacoby (21)

PRODUCT NAME(S) Ronilan Fungicide

COMPANY NAME BASF Wyandotte Corporation

SUBMISSION PURPOSE Proposed registration of peanuts and
beans uses

SHAUGHNESSY NO.	CHEMICAL & FORMULATION	% A.I.
<u>113201</u>	<u>Vinclozolin</u>	<u>50%</u>
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EEB Branch Review

Vinclozolin

100 Submission Purpose and Label Information

100.1 Submission Purpose and Pesticide Use

The registrant, BASF Wyandotte Corporation, has requested that vinclozolin (Ronilan) be registered for use as a fungicide on peanuts and phaseolus beans (succulent and dry).

100.2 Formulation Information

(from Ronilan 50W label)

Active Ingredient

3-(3,5-Dichlorophenyl)-5-ethenyl-5-methyl-2,4-

oxazolidinedione 50%

Inert Ingredients 50%

100.3 Application Methods, Directions, Rates

Proposed label directions are appended.

Generally, directions for beans are:

Two applications, 7 to 14 days apart at rates of 1 1/2 to 2 lbs, product/acre (0.75 to 1 lb ai/acre). The first treatment should be made when 20 percent of plants have one bloom. Applications can be by air or ground equipment. No more than 4 lbs product (2 lbs ai/acre) should be used in one crop season.

For peanuts,

Four applications may be necessary at a rate of 1 1/2 lbs product/acre (0.75 lbs ai/acre). Repeat treatment should be made 14 to 21 days apart. No more than 6 lbs product per acre (3 lbs ai/acre) should be used in one crop season.

100.4 Target Organisms

Beans

Botrytis blight (grey mold)
Sclerotinia blight

Peanuts

Sclerotinia blight

2

100.5 Precautionary Labeling

(from Ronilan 50W label)

"Do not apply to wetlands and other water bodies.
Do not contaminate water by cleaning of equipment
or disposal of wastes."

101 Hazard Assessment

101.1 Likelihood of Adverse Effects to Nontarget Organisms

Terrestrial Species

Available acute and subacute toxicity data indicate that technical vinclozolin is practically nontoxic to birds. A single dose oral LD₅₀ value in excess of 2,510 mg/kg is reported for the bobwhite quail. Eight-day dietary LC₅₀'s greater than 5,620 ppm have been determined for both the bobwhite quail and the mallard.

The available acute data also indicate a low mammalian toxicity for vinclozolin. Acute oral LD₅₀'s of greater than 10 g/kg and greater than 13 g/kg are established for rats.

Following an initial application of vinclozolin at a maximum rate of 1.0 lb ai per acre, expected residues on typical avian and mammalian dietary matter would range from 7 ppm on fruit and 240 ppm on sparse foliage. These residues are well below the acute toxicity values for waterfowl and upland bird species.

However, repeat treatments can be made under proposed label directions. Beans can be sprayed twice at 1 lb ai/acre, 7 days between applications. Four treatments, 14 days apart at a maximum rate of 0.75 lb ai/acre can be made on peanuts. For each crop proposed for registration, accumulated residues of vinclozolin applied at maximum rates were estimated for a variety of terrestrial wildlife dietary matter. (Based on nomograph values of Kenaga). Parameters utilized are:

	<u>Beans</u>	<u>Peanuts</u>
Applications	2	4
Rate (lb ai/acre)	1	0.75
Interval between application	7 days	14 days
Half-life*	7 days	7 days

*Half-life of the chemical will vary with type of dietary matter exposed. A 7-day half-life was chosen because it falls between the half-life of 5 days reported for strawberries (EEB Review Out: August 27, 1979 by J. Leitzke) and the half-life of 9.4 days for peaches (EEB Review Out: December 16, 1982, by M. Gessner). No additional half-life data on peanuts and beans were available from Residue Chemistry Branch (Personal communication - Mike Firestone, Ph.D.) It should be noted that a residual half-life of 16 days was reported for stonefruits, thus 7 days can be considered a "conservative" value.

Residue calculations are appended. Maximum expected accumulated residues do not approach the LC50 criterion used to indicate acute hazard to terrestrial species.

Use of vinclozolin poses a potentially significant chronic hazard to avian species. Data on avian reproduction suggest that the chemical begins to affect egg fertility at dietary concentrations of at least 5 ppm and greater. Theoretically, residues greater than 5 ppm could be retained on wildlife dietary matter contaminated during an intensive control program for peanuts (refer to accumulated residue table). There is particular concern for small avian species (i.e. passerines) that have a relatively short reproductive cycle.

The Canadian Wildlife Service indicates that vinclozolin may affect avian testicular development. As stated in the attached memo, officials have recommended that the compound not be registered in Canada; the decision based on the available reproduction data.

According to a memo (dated August 23, 1984) to H. Jacoby (PM 21) from R. Balcomb (appended), EEB has requested that BASF submit all information relevant to the avian reproduction issue, including plans for any additional research initiated from the concerns of Canadian personnel. At this time, EEB files contain no submission from BASF addressing this matter.

It should be noted that the "one-liner" data obtained from the Toxicology Branch files do not indicate effects of vinclozolin on male mammalian reproduction systems. This reviewer examined the full reviews of the mammalian data and notes that atrophied testes and/or prostate glands were observed in the 6 month feeding study on dogs and the 130 week feeding/oncogenic study on rats. These effects were found at high levels of vinclozolin. For a variety of reasons, the Toxicology Branch evaluations were "cautious" about attributing the atrophy to effects of the toxicant.

Aquatic Organisms

Unfortunately the acute toxicity data for freshwater fish are not reliable (EEB Review Out: February 20, 1980, by M. Rexrode). A precipitate formed in all the test vessels of both the bluegill and rainbow trout studies. No precipitate was reported for the aquatic invertebrate study. An LC₅₀ of 3.65 ppm was determined for Daphnia magna.

Assuming a single direct application to water, vinclozolan treatments at maximum recommended label rates would produce the following residues:

<u>Depth of water (ft)</u>	<u>Beans at 1 lb ai/acre Residues (ppm)</u>	<u>Peanuts at 0.75 lb ai/acre Residues (ppm)</u>
0.5	0.734*	0.55*
1.0	0.367*	0.276
2.0	0.183	0.138
3.0	0.122	0.092

* exceeds 1/10 the LC₅₀ of Daphnia magna

As tabulated below, the available environmental fate information indicate that vinclozolin hydrolyzes with the shortest half-lives at alkaline pH's.

<u>pH</u>	<u>Temperature</u>	
	<u>25 °C</u>	<u>35 °C</u>
3	70 days	22.5 days
6	61 hours	22.5 hours
9	12.6 min.	4.8 min.

Most aquatic organisms tolerate a pH of 6 to 9, thus a half-life of a few hours to a few days would be expected for vinclozolin in a warmwater environment (25 °C). The half-life of the chemical could be greatly extended in coldwater habitat (12 °C).

EEB cannot complete a hazard assessment until appropriate acute toxicity data on freshwater fish are provided. Once satisfactory data are submitted, the need for further testing and labeling will be determined.

101.2 Endangered Species Considerations

To fully address potential hazards to Federally Endangered/Threatened species, EEB needs the following:

- 1) More detailed information relating to effects of vinclozolin on avian reproduction.
- 2) Two basic freshwater fish acute toxicity studies.
- 3) An acute contact LD₅₀ study on honeybees.

102 Conclusions

EEB cannot concur with this request for registration of vinclozolin on peanuts and phaseolus beans. Pertinent ecological data are lacking and a hazard assessment cannot be completed. Required data include:

- I. Two acute toxicity studies on freshwater fish (preferably bluegill sunfish and rainbow trout as test species). Results of the three previously submitted fish studies showed insolubility of the technical material at most test concentrations. These studies do not provide acceptable dose-response information needed to a) determine toxicity to fish (for use in a hazard assessment for nontarget organisms including Engandered Species), b) discern further testing requirements, c) establish proper precautionary labeling of products.

The registrant should be aware of the following procedures for dealing with insoluble materials:

- a) Alternative solvents, as recommended in EPA and ASTM publications.
- b) Chemical analysis during testing to determine actual concentrations of test material.
- c) Flow-through systems, such as the Birge system of active suspension (chemical analysis must be incorporated into the study design).
- d) Testing on the end-use product since it is formulated to keep the pesticide in suspension. However results of formulation testing will support registration of the 50W product only and not other formulations.

The registrant should communicate with EEB if questions arise.

II. More detailed information on the chemical's potential effects on avian reproduction. According to the attached memos, the Canadian Wildlife Service has recommended against registration of the chemical in Canada due to potential adverse effects on avian reproduction. The registrant must contact EEB to coordinate research efforts that may have been initiated by the concerns of Canadian officials. Further testing for the Agency under Section 70-1(d) of the Guidelines (Special Tests) is in order.

III. Non-target insects will be exposed to vinclozolin under proposed and currently registered uses. Data from an acute contact LD₅₀ study on honeybees are required.

Elizabeth E. Zucker 6/27/85
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Expected Residues of Vinclozolin on Vegetation Following Repeat Applications at Maximum Label Rates

Peanut Use Pattern

	<u>Fruit</u>	<u>Seeds/ Large Insects</u>	<u>Small Insects/ Forage</u>	<u>Leaves/ Leafy crops</u>	<u>Long Grass</u>	<u>Short Rangegrass</u>
Day 0	5.5	9	45	95	82	180
14	6.9	11.3	56.3	118.8	102.5	225
28	7.2	11.8	59.1	124.7	107.7	236.3
42	7.3	11.9	59.8	126.2	108.9	239.1

Parameters Utilized

No. of applications: 4
Rate: 0.75 lbs ai/acre
Interval between applications: 14 days
Half-life of chemical: 7 days

Bean Use Pattern

	<u>Fruit</u>	<u>Seeds/ Large Insects</u>	<u>Small Insects/ Forage</u>	<u>Leaves/ Leafy crops</u>	<u>Long Grass</u>	<u>Short Rangegrass</u>
Day 0	7	12	58	125	110	240
7	10.5	18	87	187.5	165	360

Parameters Utilized

No. of applications: 2
Rate: 1 lb ai/acre
Interval between applications: 7 days
Half-life of chemical: 7 days



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 23 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Henry Jacoby
Product Manager 21
Registration Division

THRU: Harry Craven *Harry Craven*
Section Head 4
EEB

THRU: Clayton Bushong *Clayton Bushong*
Chief
EEB

SUBJECT: Ronalin (vinclozolin) effects on avian reproduction

We have received a report from the Canadian Wildlife Service (CWS) that their review of recent data submitted to them by BASF indicates effects of Ronalin on avian testicular development. Reportedly BASF is developing additional data for Canada to address this issue.

We have asked the CWS to provide us with a copy of their report.

In addition, we request that BASF be contacted and asked to provide EPA all information relevant to this issue including their plans for additional research.

Richard Balcomb

Richard Balcomb
Ecological Effects Branch
Hazard Evaluation Division



Environment
Canada

Environnement
Canada

Environmental
Conservation

Conservation de
l'environnement

September 11, 1984

Your file Votre référence

Our file Notre référence

Mr. Adrian Carter
Pesticides Division
Plants Products and Quarantine Directorate
Agriculture Canada
960 Carling Avenue
Ottawa, Ontario
K1A 0C6

Dear Adrian:

Re: Avian Reproduction and Vinclozolin (Ronilan)

In our earlier review of this product (Elliott in litt. 11 July 1983) we concluded that, based on the considerable exposure potential of this product, an avian reproduction study should be generated. As we found out later, two such studies (mallard and quail) existed but had been omitted from the data package submitted for registration. Companies should be made to realize that, by not submitting complete data packages, they are adding unnecessary delay to the evaluation process.

Enclosed is my review of the mallard reproductive study which brought to light some worrisome facts. Based on this data we recommend that vinclozolin (Ronilan) not be registered in Canada at this time. This recommendation supersedes that which was made in our review of 11 July. We believe that the effects documented here are serious enough that temporary registration should not be granted.

Should the registrant wish to pursue registration, we suggest further studies which need to be done before the product can be considered for any use pattern. Based on the results of these studies we should be able to determine whether any of the proposed use patterns are acceptable. Do not hesitate to contact me if you wish further information.

Sincerely,

Pierre Mineau

c.c.: N.Y. Khan
D.L. MacKenzie
W.K. Marshall
H.S. Thompson
W. Wandelmaier

Canada

In order to conserve energy
and resources, this paper
contains post-consumer
fibre.

À des fins de conservation
de l'énergie et des ressources
ce papier contient des
fibres recyclées.

THE EFFECT OF THE DIETARY INCLUSION OF BAS 352F ON REPRODUCTION IN THE
MALLARD DUCK
N.L. Roberts, C. Fairley, D.O. Chanter and A. McAllister
Huntingdon Research Centre
January 25, 1982

General comments regarding protocol and study quality:

- 1) The total number of eggs set for the 5 ppm group is 757 rather than 767 as reported.
- 2) Cage temperature is said to vary between 10 and 32 C°. This an unacceptably wide range which is likely to introduce variability in the bird's reproductive performance and which will tend to mask any clear compound-related effects. Note that the recommended temperature for the EPA protocol is 21 C°
- 3) Results of the diet analysis are said to be reported separately by the sponsor - those are not included here. No information is provided regarding the replenishing of food hoppers - this is a factor to be considered since the material is somewhat photolabile (Part 6, Report 2, Vol.1).
- 4) Eggs to be incubated should not be kept at room temperature as they were here. Best results are achieved when they are kept cool. EPA protocols recommend 16° and 55% RH.

Reported results:

Of acknowledged treatment-related effects, the following in my opinion are worthy of further scrutiny:

1. Egg Production:

Birds in both the 5 and 50 ppm groups laid significantly fewer eggs than the control in weeks 7 to 13 of egg laying.

\bar{x} weekly egg production:	Control: 101 (s=28)
b/w weeks 7 to 13	5 ppm: 73 (s=19)
summed for all replicates	50 ppm: 80 (s=22)

2) Fertility:

"...the chance of infertility in the high-dose group is higher than in the control group."

Weeks of egg production	Percentage of infertile eggs of eggs set per dosage group		
	Control	5 ppm	50 ppm
1-6	17.2%	24.9%	24.0%
7-13	5.1%	10.1%	41.4%
1-13	9.6%	17.5%	34.3%

...2

Treatment-related infertility:

This effect in my opinion is the most troublesome in view of its magnitude and since it appears at first glance to be dose related.

The authors of the study point out that fertility is extremely variable within dose groups but fail to explore this variability further, although they do point to an apparent link between reduced fertility and post-mortem findings of underdeveloped testes. This relationship is important enough to explore in more detail. One of the study's conclusions from post-mortem examinations is that the abnormalities observed were similar for all treatment groups. This statement is blatantly misleading since the abnormalities may be similar in appearance for all groups but certainly not in frequency. In the absence of any rigid criteria on the part of the veterinary pathologist involved, I have combined observations of "testes very small", "testes small", and "testes underdeveloped". The observations are distributed as follows:

	<u>Control</u>	<u>5 ppm</u>	<u>50 ppm</u>
Number of individuals diagnosed with small or under-developed testes.	1/12	3/12	6/12

Given the apparent dose-response indicated by the data, Bartholomew's test of frequencies for qualitatively ordered samples (J.L. Fleiss, 1973, Statistical Methods for Rates and Proportions, p.99) was performed and a treatment effect found to be valid at the .025 probability level.

Further examinations of the data show that two of the affected males were from the same pen (#12) in the 5 ppm group (please note that each replicate pen contains 2 males and 5 females). Similarly, two pens in the 50 ppm group (#11 and #18) had both their males diagnosed as having abnormal testes. It is therefore possible to compare the success of these pens with that of the "unaffected" pens. Pens where only one male was "affected" (#14 in the 5 ppm group and #2 and #13 in the 50 ppm group) cannot be used in this comparison since the number of fertile eggs obtained in those depends very much on the dominance relationships between the two males within the pen, i.e., whether the non-affected male can secure any matings. The data are divided into 4 periods (one 4-week period followed by three 3-week periods) and presented below:

...3

Dose Group	Pen	States (see text)	Percent infertility by weeks of study ¹			
			1-4	5-7	8-10	11-13
0 ppm	3	both males with normal testes	23%	2.6%	2.8%	0%
0 ppm	7		32%	27%	9.1%	19%
0 ppm	10		23%	8.1%	2.2%	0%
0 ppm	15		21%	0%	2.6%	3.3%
0 ppm	17		0%	0%	3.8%	2.9%
5 ppm	1	both males with normal testes	36%	0%	0%	0%
5 ppm	6		40%	8.3%	6.9%	0%
5 ppm	8		54%	16%	9.1%	8.2%
5 ppm	16		4.8%	0%	0%	2.9%
50 ppm	4		*100%	29%	0%	4.8%
50 ppm	9	both males with small or under- developed testes	0%	0%	8.1%	0%
5 ppm	12		45%	21%	15%	100%
50 ppm	11		25%	16%	17%	100%
50 ppm	18		4.5%	5.6%	74%	100%

¹ % values, unless otherwise indicated, are based on a mean sample size of 34 eggs (range=11-73)

* only two eggs set, both infertile

It is quite obvious that, after an initial adjustment period, (which is expected from the study design) those pens where males were apparently normal maintained a good level of fertility (no different from the control groups) until the end of the study, and this, regardless of their dosage group. However, pens where both males were eventually diagnosed as having abnormally small testes demonstrated reduced fertility by (possibly) as early as week 8 and complete infertility by week 11. Herein resides most of the between-pen variability noted in the study. Please note that the poor housing conditions (documented above) may have given rise to further variation in the base fertility level and this may obscure other meaningful trends.

Conclusion:

I conclude from the above that vinclozolin can have a dramatic impact on the male reproductive function in birds. The frequency but possibly not the severity of this effect appears to be dose-related. A "no-effect level" cannot be established with any certainty from the data provided. The authors of the study are to be criticized for not following up on their own data, since for these findings to be of real value, a more detailed post-mortem, including testes weight and histology would have been required.

In my opinion, several key questions need to be answered: 1) is this infertility reversible? 2) are young chicks at risk during the initial gonadal maturation period? Note that in most birds, the seminiferous tubules are organized and spermatogonia proliferate during the first 5 weeks of life. Primary spermatocytes first appear during weeks 5-8, secondary spermatocytes by 10 weeks onwards and spermatids appear in all seminiferous tubules

by 12 to 20 weeks of age. Actual spermatogenesis takes approximately 25 days. The stages of spermatogenesis in the duck are described in O.W. Johnson, 1966, "Quantitative features of spermatogenesis in the mallard, Anas platyrhynchos", The Auk 83: 233-239. 3) is there a no-effect level? If one can be established from further studies, more information will be needed on likely environmental concentrations, especially levels in turf, following application. As outlined in our previous evaluation, exposure is likely given the repeated nature of the treatment and the slight bio-accumulatory nature of this compound. 4) is the parent compound or one of the metabolites responsible for the effect? 5) is the duck the best model for this effect?

It would seem that, at least; the Mallard Duck is more sensitive than the Bobwhite Quail. A companion study ("The effect of the dietary inclusion of BAS 352F on reproduction in the Bobwhite Quail" Huntingdon Research Centre, January 28, 1982) found a somewhat higher incidence of infertility in the dosed groups but this difference was not statistically valid. (Note that the summary is incorrect in alluding to an increase in fertility.) Inter-pen, within-group fertility is again said to be highly variable which is not surprising in view of the same conditions of temperature (fluctuating between 10 and 32°C). Post-mortem examinations made no mention of reduced testis size. This study, although meaningless by itself, provides a clue that the mechanism is common to both groups of birds.

Recommendations:

We recommend that, until the proponent can answer the above questions satisfactorily, Vinclozolin should not be registered in Canada. The impact on male reproduction, (without a clear indication of what the no-effect level is) as well as the apparent effect of this product on egg production at the lowest dose tested (5 ppm) are strong contra-indications against the registration of this product for the wide use-pattern anticipated. Should the registrant wish to proceed with registration, much more rigorous data will be needed to ascertain the safety of each and every use-pattern. No-effect levels will need to be clearly demonstrated, both for the male and female reproductive effects and exposure will clearly have to be defined for each use-pattern anticipated. We invite the registrant to discuss with us the design of any study they wish to undertake. Some of the questions that were asked above (e.g. the reversibility and age sensitivity of the male effect) cannot be answered through the routine EPA protocols.

Pierre Mineau

RIN 5715 - 93

VINCLOZOLIN EEB REVIEWS

Page _____ is not included in this copy.

Pages 15 through 18 are not included.

The material not included contains the following type of information:

- _____ Identity of product inert ingredients.
- _____ Identity of product impurities.
- _____ Description of the product manufacturing process.
- _____ Description of quality control procedures.
- _____ Identity of the source of product ingredients.
- _____ Sales or other commercial/financial information.
- ✓ _____ A draft product label.
- _____ The product confidential statement of formula.
- _____ Information about a pending registration action.
- _____ FIFRA registration data.
- _____ The document is a duplicate of page(s) _____.
- _____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.